

D-lactate and SCUBE-1 levels in critically ill patients

D-lactate, SCUBE-1 in ICU cases

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Abstract

Aim: Critical illness in the emergency department (ED) of a hospital requires rapid assessment and intervention. This study aimed to investigate the diagnostic and prognostic levels of D-lactate and SCUBE-1 in critically ill patients being admitted to the ED.

Material and Methods: This prospective observational case-control study consisted of 45 critically ill patients and 45 healthy controls. Serum D-lactate and SCUBE-1 levels were measured upon admission to the ED, and clinical scores (APACHE II, GCS, RTS) were calculated for critically ill patients. The primary outcome was 28-day mortality.

Results: Both D-lactate and SCUBE-1 levels were significantly higher in critically ill patients as compared to controls ($p < 0.001$). In multivariate logistic regression analysis, SCUBE-1 (OR=2.16, 95%CI:1.65-3.43, $p < 0.001$) and D-lactate (OR=1.86, 95%CI:1.11-2.41, $p = 0.012$) were independent predictors of mortality. ROC analysis revealed that SCUBE-1 > 43 ng/mL predicted mortality with 56.2% sensitivity and 72.4% specificity, while D-lactate > 279 mmol/L showed 51.5% sensitivity and 68.3% specificity. D-lactate and SCUBE-1 levels are promising biomarkers for the prediction of mortality in critically ill ED patients.

Discussion: These markers, when used in conjunction with clinical scoring systems, may prove useful when risk stratification and guide management decisions are made in the ED.

Keywords

D-lactate, SCUBE-1, critical illness, emergency department, mortality biomarkers

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Introduction

A critically ill patient is defined as having unstable basic vital functions, is receiving supportive treatment, or whose general condition is expected to deteriorate [1,2]. With the rise in the number of patients admitted to emergency departments (ED), there has been a corresponding increase in the number of critically ill patients, and reports indicate a 79% rise in the proportion of critically ill patients among all ED admissions [3,4]. Survival in these patients is primarily determined by the severity of the acute illness upon admission and the quality of care provided throughout the course of the treatment, [5,6]. Rapid assessment and intervention are crucial, and many scoring systems have been developed to assist in determining treatment priorities [1, 3]. The role of the ED is resuscitation and initial assessment in the care of critically ill patients, rather than providing continuous longitudinal care, [7]. Lactic acid exists as two optical enantiomers: L-lactic acid and D-lactic acid, [8, 9]. Humans normally produce very little D-lactate because they lack the enzyme D-lactate dehydrogenase (D-LDH) [8,10]. However, D-lactate can be produced endogenously in limited amounts in tissues such as the brain and the lens of the eye via the methylglyoxal pathway [8,11]. Furthermore, D-lactate is produced in certain amounts by gastrointestinal bacteria, but blood levels increase due to antibiotic use, short bowel syndrome, inflammatory bowel disease (IBD), metabolic disorders, autoimmune conditions, sepsis, and psychiatric and neurological diseases that cause an increase in D-lactate-producing bacteria, such as dysbiosis [8-10,12]. D-lactate may be exogenously increased as a result of fermented foods, propylene glycol-containing drugs, or Ringer's lactate use [8,13]. However, when D-lactate is formed, it is metabolized to pyruvate by D-2-hydroxy acid dehydrogenase (D-2-HDH) in the liver and kidney [8,12,13].

SCUBE-1 (signal peptide-CUB-epidermal growth factor [EGF] domain-containing protein 1) is a cell surface glycoprotein expressed during early embryogenesis and found in platelets and endothelial cells, [14-16]. SCUBE-1 is involved in the process of developmental and pathologic angiogenesis [14-17], and has been demonstrated by in situ hybridization in vascular endothelial cells. It is abundant in several highly vascularized tissues, such as the liver, kidney, lung, spleen, and brain [14,16,18], and is produced and stored in platelets [18]. Plasma SCUBE-1 has been shown to bind platelets together to form thrombi and plays a critical role in arterial thrombosis, [16,17,18]. Clinical studies have shown that plasma SCUBE-1 levels increase in ischemic conditions, such as acute coronary syndrome and acute ischemic stroke, and may be a biomarker of platelet activation [14,15,18].

Many scoring systems have been developed to determine the severity of illness and predict mortality in critically ill patients. However, no clinical tool has been validated to predict disease severity and mortality among patients considered to require critical care in the ED. Due to this shortcoming, researchers have turned to finding new biochemical markers for strengthening scoring systems. This study aims to contribute to this research by investigating the efficacy of serum D-lactate and SCUBE-1 levels in predicting disease severity and prognosis in critically ill patients admitted to the ED.

Materials and Methods

Study Design and Setting

This observational and prospective study was conducted in the Emergency Department (ED) of Kanuni Sultan Süleyman Training and Research Hospital, a tertiary care center. The ED includes a Level 3 emergency intensive care unit comprising seven beds and managed by emergency medicine specialists, where all patients enrolled in the study were monitored. The study period spanned from July 2019 to January 2020, during which the ED admitted approximately 30,000 patients per month. All trauma patients presenting to the ED were treated according to Advanced Trauma Life Support (ATLS) protocols, while non-trauma patients were managed in line with Advanced Cardiac Life Support (ACLS) guidelines. Informed consent was obtained from the relatives of all patients. The study was based on blood samples collected from critically ill patients at the time of initial presentation, and the patient flow chart is shown in Figure 1.

Various data were recorded, including patients' demographic characteristics, medical history, vital signs, laboratory findings, and, for trauma patients, the mechanism of injury, Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Revised Trauma Score (RTS), shock index, and mortality status. Trauma scoring systems such as the Glasgow Coma Score (GCS), Injury Severity Score (ISS), and Abbreviated Injury Scale (AIS) were utilized to assess the severity of patients' clinical conditions. Critical patients were categorized into seven groups based on their ED diagnoses: central nervous system, cardiovascular system, respiratory system, gastrointestinal system/metabolic, sepsis, trauma, and others. Clinical outcomes of these patients (ED length of stay, intensive care unit (ICU) or ward admission, ED and ICU mortality) were also documented.

Treatment for critical patients was initiated according to ACLS/ATLS protocols, and blood samples collected upon ED admission were placed in Ethylenediaminetetraacetic acid (EDTA) tubes. After centrifugation at 2800 rpm for 20 minutes at 4°C, plasma samples were transferred to Eppendorf tubes and stored at -80°C until analysis. Scube-1 and D-lactate levels were measured in duplicate using enzyme-linked immunosorbent assay (My-BioSource MBS044526; MyBioSource, Inc., San Diego, California). Scube-1 levels were expressed in nanograms (ng)/mL, while D-lactate levels were expressed in millimoles (mmol)/L.

Statistical Analysis

In the study data, numerical values were expressed as mean $\pm$ standard deviation and minimum-maximum values. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of all variables. The Chi-squared correspondence test was used to evaluate nominal data between groups, while the Student's t-test was used for parametric variables in the clinical study. The Kruskal-Wallis H test and the Mann-Whitney U test were used in statistical evaluations according to whether the nonparametric variables were categorical (nominal or ordinal) or numerical independent groups. The Spearman correlation test was used to evaluate the correlation between D-lactate and SCUBE-1 levels in the data set, according to mortality. These results of the critical care patients were

evaluated with the ROC (Receiver Operating Characteristics) curve according to the clinical results of D-lactate and SCUBE-1 blood values. The regression analysis method was used to assess the effect of patient diagnoses and previous diseases on SCUBE-1 and D-lactate levels in the data set. The results were evaluated for a significance level of $p < 0.05$. According to the sample calculation made with G-Power, assuming an alpha error of 5%, a working power of 80%, and a loss of 20%, it was determined that 90 patients would be sufficient for the study.

Ethical Approval

The present study was approved by the ethics committee of Kanuni Sultan Suleyman Training and Research Hospital (Date: 2019-01-11, No: 2019-1/11).

The study was registered in ClinicalTrials.gov (NCT06704438).

Results

During the study period, 80 volunteer critically ill patients were assessed for eligibility, and 35 were excluded for the following reasons: 13 refused to participate, eight could not calculate the scoring system, seven had incompatible blood samples, five lacked data, and two were under 18 years of age. The final sample consisted of 45 critically ill patients (25 (55.6%) males and 20 (44.4%) females) and 45 healthy volunteers in the control group (23 (51.1%) males and 22 (48.9%) females). The mean age of the critically ill patients was 64.8 ± 21.4 years. The baseline characteristics of the participants are shown in Table 1. The most common diagnoses in critically ill patients were respiratory system diseases (n:15) and trauma (n:11). 28-day mortality was 40% (n:18). APACHE II score was 18.6 ± 9.1 in deceased critically ill patients, which was higher than in critically ill patients (16.3 ± 8.2 in critically ill patients). SCUBE-1 level at admission was 124.5 ± 85.6 in the deceased group and 53.3 ± 9.8 in the surviving group, which was significantly lower ($p < 0.001$). The diagnoses, clinical scores, and laboratory values of critically ill patients are shown in Table 1. Variables found to be significant in univariate logistic regression analysis were included in the multivariate logistic regression model. In multivariate logistic regression analysis, SCUBE-1 (OR=2.16, 95%CI:1.65-3.43, $p < 0.001$), D-lactate (OR=1.86, 95%CI:1.11-2.41, $p = 0.012$), GCS (OR=0.68, 95%CI:0.57-0.84, $p < 0.001$), and APACHE II (OR=1.39, 95%CI:1.06-3.79, $p = 0.031$) scores were independent predictors of mortality in critically ill patients in the ED (Table 2). The cut-off value of D-lactate and SCUBE-1 levels for predicting mortality in critically ill patients was

Table 1. Comparison of demographic characteristics of critically ill patients and factors related to clinical outcome

Variables	Outcome				P-value
	Control group (n=45)	All critically ill patients (n=45)	Survival to discharge (n=27)	Death (n=18)	
Age in years	63.6±17.2	64.8±21.4			0.530
Gender					0.088
Male	23 (51.1%)	25 (55.6%)			
Female	22 (55.6%)	20 (44.4%)			
Scube-1 (ng/mL) (median)	49	61			<0.001
D-lactate (mmol/L) (median)	274	341			<0.001
Clinical scoring					
RTS		6.216±1.939	5.975±1.867	6.324±1.988	0.087
APACHE II score		18(10-34)	16(10-30)	21(10-34)	<0.001*
GCS		13(3-15)	13(7-15)	12(3-15)	0.823
GCS (9-15)		32(71.1%)	24(88.9%)	8(44.4%)	0.096
GCS (3-8)		13(28.9%)	10(55.6%)	10(11.1%)	<0.001*
Shock index		1.10±0.49	1.04±0.57	1.21±0.52	0.315
Shock index<1		20(17.3%)	13(31.7%)	7(14.3%)	0.056
Shock index≥1		25(60.8%)	14(78.0%)	11(57.1%)	0.118
Top five primary diagnoses, n (%)					
Respiratory System		20(44.4%)	12(44.4%)	8(44.4%)	0.573
Trauma		11(24.4%)	5(18.5%)	6(33.3%)	0.021*
Metabolic/ Gastrointestinal System		6(13.3%)	5(18.5%)	1(5.6%)	0.058
Cardiovascular System		3(6.6%)	2(7.4%)	1(5.6%)	
Sepsis		3(6.6%)	1(3.7%)	2(11.1%)	
Laboratory parameters					
pH		7.18±0.29	7.25±0.27	7.12±0.30	<0.001*
Lactate, mmol/L		4.1(1.0-6.5)	3.1 (1.6-5.7)	5.4 (3.4-7.7)	<0.001*
Neutrophil, (x10 ⁹ /L)		6.30±2.54	5.84±1.50	6.52±2.66	0.034*
Lymphocyte, (x10 ⁹ /L)		2.19±0.65	2.30±0.79	2.13±0.60	0.076
Procalcitonin		18.4± 43.6	17.9± 39.1	20.4± 44.2	0.106
NLR		3.11±1.20	2.36±0.79	3.27±1.21	<0.001*
Scube-1 (ng/mL) (median)		61	54	61.5	<0.001*
D-lactate (mmol/L) (median)		341	277	352.5	<0.001*

Data is presented as mean ± standard deviation, median, and 25th–75th percentiles or n (%). *p-value < 0.05, RTS: Revised Trauma Score, GKS: Glasgow Coma Scale, Apache II: Acute Physiology and Chronic Health Assessment II, NLR: neutrophil-lymphocyte ratio.

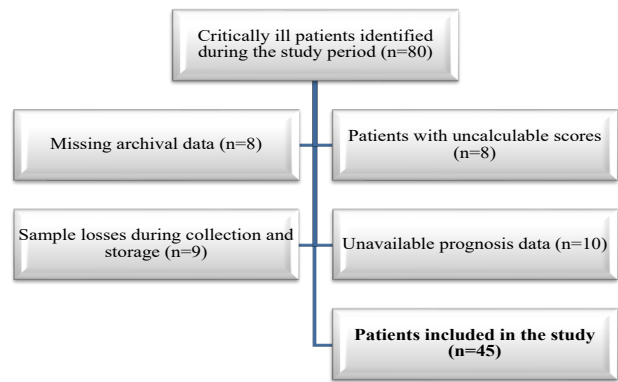


Figure 1. Patient flow chart

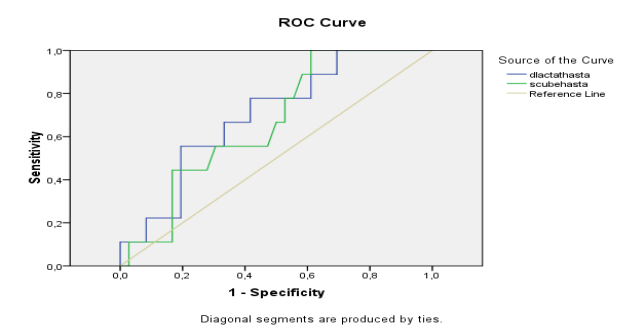


Figure 2. Receiver-operating characteristic curves of D-lactate and SCUBE-1 to predict mortality in critically ill patients

Table 2. Univariate and multivariate analysis of predictive factors of mortality in critically ill patients

Variables	Univariate logistic regression		Multivariate logistic regression	
	OR (95% CI)	P-value	OR (95% CI)	P-value
APACHE II	0.59 (0.36–0.83)	0.015	0.67 (0.41–0.92)	0.013*
GKS (3–8)	0.72 (0.59–0.86)	<0.001	0.68 (0.56–0.84)	0.004*
Trauma	1.13 (1.04–2.64)	0.025	1.07 (0.89–3.56)	0.276
pH	1.64 (1.14–2.28)	<0.001	1.34 (0.91–5.78)	0.094
Neutrophil, (x10 ⁹ /L)	0.81 (0.75–0.87)	0.042	0.83 (0.75–0.90)	0.157
NLR	1.71 (1.16–2.32)	<0.001	1.86 (1.11–2.41)	0.076
Lactate, mmol/L	1.22 (1.05–2.65)	<0.001	1.09 (1.06–3.79)	0.174
Scube-1 (ng/mL)	2.13 (1.72–3.97)	<0.001	2.16 (1.65–3.43)	<0.001*
D-lactate (mmol/L)	1.72 (1.09–2.86)	<0.001	1.86 (1.11–2.41)	0.012*

determined using Receiver Operating Characteristics (ROC) analysis (Fig. 2). It was discovered that an SCUBE-1 level of more than 43 ng/mL predicted mortality in critically ill patients with 56.2% sensitivity and 72.4% specificity.

Discussion

Rapid assessment and intervention are important to reduce mortality in critically ill patients admitted to the ED, [10]. In the ED, deterioration of the critical patient’s condition or unexpected death usually precedes abnormalities in vital signs [3,4]. The causes of death are potentially treatable, and treatment is effective if intervention is made in time, [3,4]. Early diagnosis is therefore crucial for early intervention. While many laboratory parameters, scoring systems, and imaging methods have, to date, been used to determine possibly fatal diagnoses in critically ill patients [2,4,6,10], no single valid method is yet available. As the use of new markers, together with scoring systems, may be useful in terms of prognosis prediction and treatment management, this study investigated the effect of D-lactate and SCUBE-1 levels on the survival of critically ill patients in the ED until discharge. To our knowledge, this is the first study to examine D-lactate and SCUBE-1 levels as prognosis predictors in critically ill patients. The study has determined that both D-Lactate and SCUBE-1 levels were statistically significantly higher in critically ill patients when compared to the control group (p<0.001). SCUBE-1 (AUC=0.725, 95% CI: 0.491-0.839) predicted mortality in critically ill patients with 56.2% sensitivity and 72.4% specificity, while D-lactate (AUC=0.698, 95% CI: 0.521-0.874) predicted mortality with 51.5% sensitivity and 68.3% specificity. These results suggest that both D-lactate and SCUBE-1 are predictive markers for diagnosis and mortality in critically ill patients in the ED. In critically ill patients, bacterial translocation and epithelial damage usually occur as a result of inadequate oxygenation of the intestinal mucosa, leading to increased production and absorption of D-lactate [8,11]. Restrepo-Álvarez et al. emphasized that intestinal permeability increased in patients with sepsis [19]. Murray et al. reported that D-lactate levels increased in patients with intestinal ischemia, and Poeze et al. and Jørgensen et al. showed that D-lactate increased in critically ill patients with sepsis and was associated with the severity of the disease [8,20-22]. Other studies have also demonstrated that D-lactate increased due

to intestinal ischemia after abdominal surgery, [23]. This study has determined that D-lactate levels were high in critically ill patients and were even an indicator of mortality. These results suggest that intestinal ischemia is present in critically ill patients with higher D-lactate levels. It has been suggested that SCUBE-1 is abundantly expressed in human platelets, stored in α-granules, and released when the platelets are stimulated, [17,18]. In a study by Dai et al., it was shown that SCUBE-1 levels increased in 152 patients with cerebral and coronary thrombi, indicating its active role in thrombus formation. Other animal studies have also demonstrated that SCUBE-1 is involved in arterial thrombus formation, [18]. Toprak et al. reported that SCUBE-1 levels were significantly higher in 553 COVID-19 patients with a pro-thrombotic predisposition as compared to a control group, [15]. Additionally, Erdogan et al. found that SCUBE-1 levels correlated with the severity of sepsis and served as an indicator of mortality in a study of 187 patients with sepsis in which there was an imbalance in coagulation and fibrinolytic systems [24]. This study has also found elevated SCUBE-1 levels in critically ill patients compared to healthy subjects, supporting such elevated levels as a predictive marker of mortality. These results suggest that there is an impairment in coagulation and fibrinolytic systems in critically ill patients admitted to the ED. In a study conducted across 90 hospitals with 50,322 critically ill patients, Chalfin et al. found that the APACHE II score of deceased patients was 16.3 points higher than that of survivors [3]. Many similar studies have also reported that a high APACHE II score is an indicator of mortality [2,5,6]. Consistent with these results, our study also identifies a high APACHE II score as an indicator of mortality in critically ill patients admitted to the ED. The most significant aspect of our study is that it is the first prospective study to investigate D-lactate and SCUBE-1 as predictive factors for mortality in critically ill patients who have been admitted to an ED. However, the study does have certain limitations, the first being that the study was conducted at a single center with a relatively small number of patients. A second limitation was that only D-lactate and SCUBE-1 levels at the time of ED admission were examined, and no controls were included. Thirdly, other commonly used scoring systems were not considered. Lastly, the relationship between D-lactate and SCUBE-1 was not explored with the scoring systems and mortality in critically ill

patients.

Limitations

This study has several limitations. First, the relatively small sample size may restrict the generalizability of the findings. Second, it was conducted in a single-center setting, which may limit the external validity of the results. Third, critically ill patients inherently exhibit heterogeneity in comorbid conditions, therapeutic approaches, and disease severity. Additionally, the cross-sectional nature of the study does not allow for establishing causality; however, elevated D-lactate and SCUBE-1 levels may serve as prognostic indicators of increased mortality and support earlier ICU admission decisions in critically ill patients. Therefore, larger multicenter prospective studies are required to validate the diagnostic and prognostic value of D-lactate and SCUBE-1 in critically ill patients.

Conclusion

In conclusion, it was found that D-lactate and SCUBE-1 are predictive markers for diagnosis and mortality in critically ill patients in EDs. D-lactate and SCUBE-1 may be promising markers for predicting mortality in critically ill patients and could be used in conjunction with scoring systems in EDs and intensive care units. However, more extensive prospective studies are needed to confirm these findings.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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